Eurographics Workshop on Visual Computing for Biology and Medicine (2019)
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Visual Exploration of Large Normal Mode Spaces to Study Protein Flexibility

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Abstract

The extended structural biology dogma links protein 3D structure, through protein dynamics, to protein function. Transmembrane proteins or enzymes assume the role of carrying or binding small metabolites using a route (called tunnel) within the protein structure.

Throughout the transport or binding process, the protein undergoes geometrical adjustments, changing its tunnel shape and thus regulating its function. These functional changes happen on large time scales that are often too long to be captured with regular Molecular Dynamics (MD) simulations.

*In focusing on the intrinsic dynamics of a protein, we probe the possible macromolecule motions and thus isolate a subspace where structure pliancy could represent a functional movement. However, the yielded high-dimensional space is too complex to be analyzed exhaustively. Therefore, to identify only the relevant motions, we tie protein dynamics to protein tunnel changes. We aim at developing a tool for interactive exploration of the effect of protein flexibility on its tunnels. The tunnels will enable the quick and flexible exploration of individual modes and their dynamics with relevance for the protein function. Once an interesting motion is identified, the exploration of possible normal mode combinations is steered via a visualization-based recommendation system. This helps to quickly identify a narrow, yet relevant set of normal modes that can be investigated in details. We use Coarse-Grained (CG) Normal Mode Analysis (NMA) to investigate the effect of protein intrinsic dynamics on its tunnel spatial properties. Calculation of low frequency vibrational normal modes is known to describe functionally relevant protein motions [BK85]. NMA calculations are faster to compute and grant probing of structural changes happening beyond regular MD simulation timescales. We use CAVER Analyst [JBB*18] to display their deformations following the protein pliancy as well as analyzing tunnel features within the normal mode subspace. CG NMA computes only the flexibility of the protein carbon alpha atoms. To be able to obtain the tunnel, we reconstructed the amino acid side chains based on the overall deformation of their corresponding carbon alpha atom.*

To explore the effect of protein flexibility on its tunnel of interest we generated conformations following a range of amplitudes and normal modes. The tunnel is computed on the initial structure and reconstructed on each conformation based on its residues overall deformation.

Our solution is embedded inside CAVER Analyst framework and enables further tunnel analyses and exploration from NMA, without the need to use prior computationally costly MD simulations.

CCS Concepts

• ***Applied computing*** → ***Bioinformatics; Molecular structural biology;*** • ***Human-centered computing*** → ***Scientific visualization;***

References

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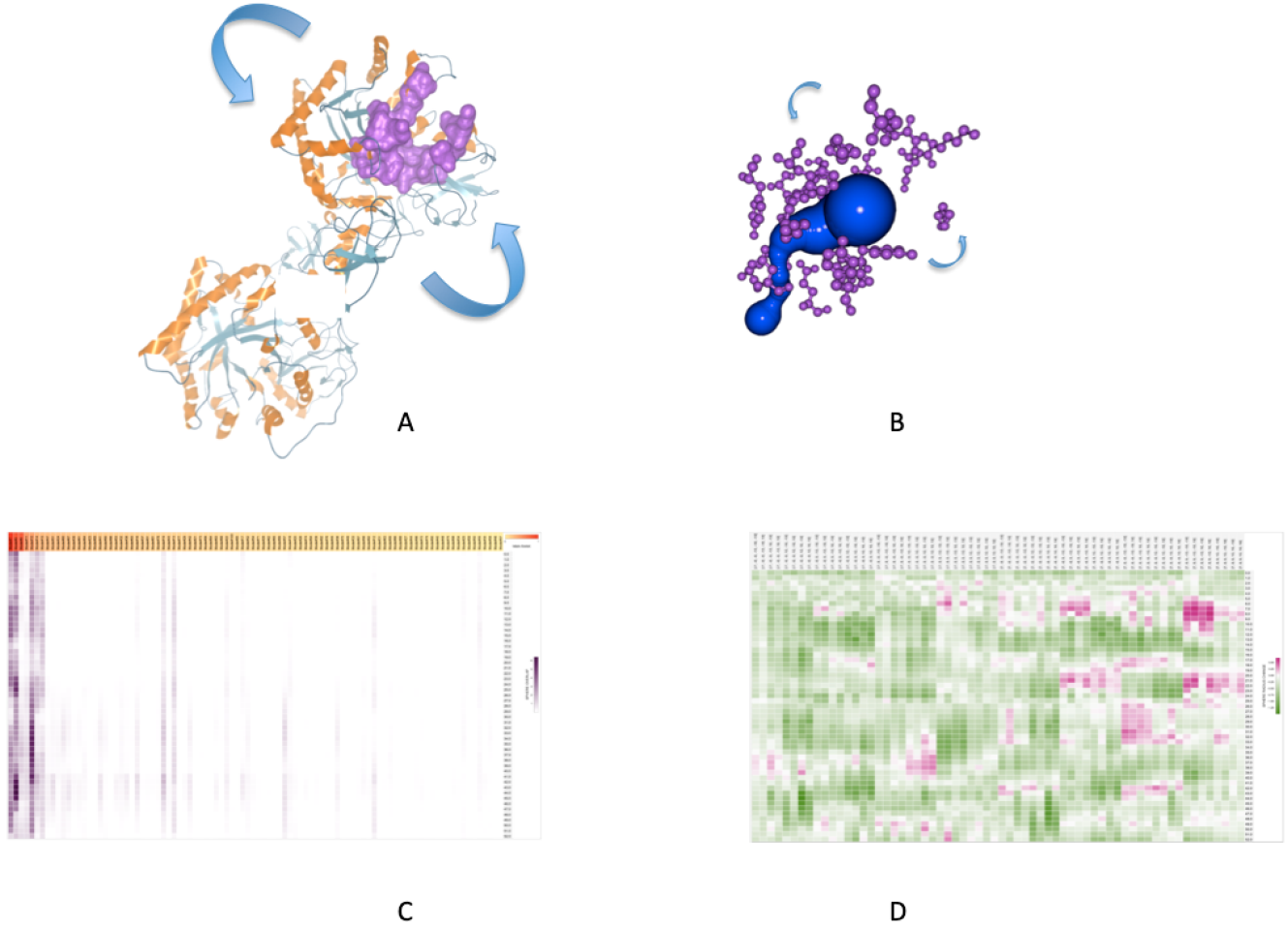

Figure 1: ***Tunnel analysis following the normal mode deformations*** *(A) Protein structure with catalytic cavity residues represented using purple surface. Cavity residues are taken from [SMG*15]. Secondary structure alpha helices are shown in orange and beta sheets in blue. (B) Magnified catalytic cavity with purple residues around the computed tunnel of interest. Blue arrows indicate the structure chain A intrinsic dynamics with the upper domain rotating on itself anticlockwise. (C) Single Normal Mode View. Columns correspond to the individual modes while rows indicate the tunnel sphere, from the inside of the protein (top) to the outer environment (bottom). Values are displayed on the chart with strong purple representing high mode involvement. (D) Combined Normal Mode View. Columns describe the mode phases representing arbitrary directions for each of the normal mode in the dataset, while rows indicate the tunnel spheres from the inside of the protein (top) to the outer environment (bottom). Values are displayed on the chart, with strong violet representing an increase and green a decrease of the tunnel radius.*